ANESTHESIOLOGY

Isoelectric Electroencephalography in Infants and Toddlers during Anesthesia for Surgery: An International Observational Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In adults, intraoperative episodes of isoelectric encephalogram (commonly termed burst suppression) are associated with hypotension and postoperative delirium
- The variation in prevalence of isoelectric events during routine general anesthesia and surgery in pediatric patients worldwide is not known

What This Article Tells Us That Is New

- Isoelectric events occurred in about a third of patients, but varied widely between sites
- Increased isoelectric events occurred with increased sevoflurane concentrations, younger age, propofol boluses, and endotracheal tube use
- Isoelectric events were associated with hypotension, but not associated with emergence agitation

ABSTRACT

Background: Intraoperative isoelectric electroencephalography (EEG) has been associated with hypotension and postoperative delirium in adults. This international prospective observational study sought to determine the prevalence of isoelectric EEG in young children during anesthesia. The authors hypothesized that the prevalence of isoelectric events would be common worldwide and associated with certain anesthetic practices and intraoperative hypotension.

Methods: Fifteen hospitals enrolled patients age 36 months or younger for surgery using sevoflurane or propofol anesthetic. Frontal four-channel EEG was recorded for isoelectric events. Demographics, anesthetic, emergence behavior, and Pediatric Quality of Life variables were analyzed for association with isoelectric events.

Results: Isoelectric events occurred in 32% (206 of 648) of patients, varied significantly among sites (9 to 88%), and were most prevalent during preincision (117 of 628; 19%) and surgical maintenance (117 of 643; 18%). Isoelectric events were more likely with infants younger than 3 months (odds ratio, 4.4; 95% CI, 2.57 to 7.4; $P < 0.001$), endotracheal tube use (odds ratio, 1.78; 95% CI, 1.16 to 2.73; $P = 0.008$), and propofol bolus for airway placement after sevoflurane induction (odds ratio, 2.92; 95% CI, 1.78 to 4.8; $P < 0.001$), and less likely with use of muscle relaxant for intubation (odds ratio, 0.67; 95% CI, 0.46 to 0.99; $P = 0.046$]. Expired sevoflurane was higher in patients with isoelectric events during preincision (mean difference, 0.2%; 95% CI, 0.1 to 0.4; $P = 0.005$) and surgical maintenance (mean difference, 0.2%; 95% CI, 0.1 to 0.3; $P = 0.002$). Isoelectric events were associated with moderate (8 of 12, 67%) and severe hypotension (11 of 18, 61%) during preincision (odds ratio, 4.6; 95% CI, 1.30 to 16.1; $P = 0.018$) (odds ratio, 3.54; 95% CI, 1.27 to 9.9; $P = 0.015$) and surgical maintenance (odds ratio, 3.64; 95% CI, 1.71 to 7.8; $P = 0.001$) (odds ratio, 7.1; 95% CI, 1.78 to 28.1; $P = 0.005$), and lower Pediatric Quality of Life scores at baseline in patients 0 to 12 months (median of differences, –3.5; 95% CI, –6.2 to –0.7; $P = 0.008$) and 25 to 36 months (median of differences, –6.3; 95% CI, –10.4 to –2.1; $P = 0.003$) and 30-day follow-up in 0 to 12 months (median of differences, –2.8; 95% CI, –4.9 to 0; $P = 0.036$). Isoelectric events were not associated with emergence behavior or anesthetic (sevoflurane *vs.* propofol).

Conclusions: Isoelectric events were common worldwide in young children during anesthesia and associated with age, specific anesthetic practices, and intraoperative hypotension.

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Sevoflurane and propofol are the most commonly used drugs for maintenance of inhalational and intravenous anesthesia in the pediatric population. Their dosing is based on population pharmacokinetic models (*e.g.*, minimum alveolar concentration, target-controlled infusion)

This article is featured in "This Month in Anesthesiology," page A1. This article has an audio podcast. This article has a visual abstract available in the online version. Preliminary data presented in this article have been presented as an abstract at the International Anesthesia Research Society Annual Meeting, May 14, 2021.

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and cardiorespiratory monitoring, neither of which directly reflects the patient's brain response to these drugs.[1] Electroencephalography (EEG) provides a noninvasive method to monitor changes in brain electrical activity that can reflect brain drug levels, as EEG waveforms change predictably with propofol and sevoflurane dose.[2] Increased dose leads to an initial increase in EEG amplitude and progressively decreased frequency, until isoelectric EEG occurs where amplitude and frequency are close to zero, indicating an electrically inactive neocortex.[1]

Isoelectric EEG has been associated with intraoperative hypotension and postoperative delirium in adults.[3–5] In contrast, this association with delirium has not been shown in children.[6] Two single-center studies showed that in infants and toddlers receiving anesthesia with sevoflurane or propofol, the incidence of isoelectric EEG ranged from 51 to 63%.[7,8] It is unclear whether isoelectric EEG is common during sevoflurane or propofol-based anesthesia in infants and toddlers across the world or is associated with certain anesthetic practices, intraoperative adverse events, and postoperative outcomes.

The primary aim of our multicenter prospective observational study was to determine the prevalence of isoelectric events in infants and toddlers undergoing routine surgeries. The secondary aims were to determine demographic and anesthetic variables, adverse intraoperative events, and postoperative outcomes associated with isoelectric EEG. We hypothesized that the prevalence of isoelectric events would be common worldwide and associated with certain anesthetic practices and intraoperative hypotension.

Materials and Methods

Study Design

This 15-center prospective observational cross-sectional study (ClinicalTrials.org NCT03432351; Principal Investigator: Ian Yuan; registered February 14, 2018) was conducted in the research consortium (Brain Anesthesia Infant Network; Australia: Royal Children's Hospital, Melbourne; Perth Children's Hospital, Perth; The Children's Hospital at Westmead, Sydney; China: Beijing Children's Hospital, Beijing; Guangzhou Women and Children's Medical Center, Guangzhou; Shanghai Children's Medical Center, Shanghai; Shengjing Hospital of China Medical University, Shenyang; Sichuan Provincial People's Hospital, Chengdu; Yuying Children's Hospital of Wenzhou Medical University, Wenzhou; West China Hospital Sichuan University, Chengdu; Europe: Erasmus Medical Center Sophia Children's Hospital, Rotterdam, The Netherlands; University of Geneva, Geneva, Switzerland; United States: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Children's Medical Center Dallas, Dallas, Texas).

Each site obtained institutional review board approval, with The Children's Hospital of Philadelphia serving as the data coordinating center. All sites agreed to a common case report form and statistical analysis plan *a priori*.[9] This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[10]

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Patients

Each site targeted 50 evaluable patients evenly divided into five age groups by month: 0 to 3, 4 to 6, 7 to 12, 13 to 18, and 19 to 36. These age groups were defined *a priori* and selected to efficiently achieve an even age distribution among sites, as well as to conform to previous studies that have defined normative developmental physiologic values (*e.g.*, EEG features, sevoflurane and propofol pharmacokinetics).[11–13] A consecutive sampling approach was performed. After screening for eligibility, the patient family or caregiver was approached preoperatively to obtain written informed consent.

Inclusion criteria were the following: (1) age 36 months or younger; (2) postmenstrual age 36 weeks or older on the day of surgery; (3) undergoing general anesthesia for surgery scheduled for greater than 30 min; (4) anesthetic maintenance with sevoflurane or propofol; and (5) airway management with laryngeal mask airway or endotracheal tube (ETT).

Exclusion criteria were as follows: (1) American Society of Anesthesiologists (ASA) Physical Status greater than III; (2) frontal brain malformations; (3) history of abnormal EEG or severe neurologic abnormalities; (4) emergency surgery or surgery of the head, heart, or brain; (5) recent sedative infusion (less than 24 h) including propofol, morphine, fentanyl, midazolam, ketamine, and dexmedetomidine; or (6) use of ketamine during the anesthetic.

EEG Recording

The EEG (Sedline; Masimo Inc.; USA) utilizes a disposable sensor on the forehead that records four channels corresponding to Fp1-aFz, Fp2-aFz, F7-aFz, and F8-aFz in the international EEG nomenclature. EEG recording started in the operating room before induction and ended after removal of the airway device. The anesthesia team was blinded to the EEG data. The research team monitored the EEG signals for waveform quality and impedance less than 14 kΩ. The EEG file was stored in European Data Format and transferred to The Children's Hospital of Philadelphia for offline analysis.

Anesthetic Management

For induction, patients with an IV catheter received propofol bolus, and patients without an IV catheter received sevoflurane inhalation by mask. For anesthetic maintenance, propofol infusion was administered by manual infusion or target-controlled infusion, whereas sevoflurane was inhaled through laryngeal mask airway or ETT. For patients who received sevoflurane for induction followed by propofol for maintenance, it was possible to have residual sevoflurane in their brain even after discontinuation of sevoflurane. Anesthetic dose, airway management, other medications (*e.g.*, opioids, muscle relaxant), and local and/or regional anesthesia (*e.g.*, lidocaine, bupivacaine) were at the discretion of the anesthesia and surgical team and were recorded for analysis.

Demographic and Anesthetic Explanatory Variables

Patient variables included postmenstrual age at study, premature birth (postmenstrual age less than 37 weeks at birth), ASA Physical Status, sex, race or ethnicity, and site.

Surgical variables included general or specialty (*e.g.*, urology) surgery.

Time variables included recording the following five timestamps: induction, intubation, incision, end of surgical closure, and extubation. These five timestamps formed four anesthetic phases: (1) induction, induction to intubation; (2) preincision, intubation to incision; (3) surgical maintenance, incision to end of surgical closure; and (4) emergence, end of surgical closure to extubation.

Anesthetic variables included midazolam premedication (yes or no), induction and maintenance technique (inhalation sevoflurane or IV propofol), expired sevoflurane concentration (percentage) during preincision and surgical maintenance phases, use of neuromuscular blockade for intubation (yes or no), opioids (yes or no), regional anesthesia (yes or no), propofol bolus after sevoflurane induction for ETT or laryngeal mask airway placement (yes or no and dose milligram per kilogram), propofol bolus dose (milligram per kilogram) for IV induction, and airway device (laryngeal mask airway or ETT).

All data were recorded in Research Electronic Data Capture (Vanderbilt University, USA).

Outcomes of Interest

Isoelectric EEG. A customized MATLAB program (Mathworks Corp., USA) was used to remove EEG artifact and identify isoelectric events. The MATLAB program for determining isoelectric events was validated in a previous study of the same age cohort as the current study.[8] In the current study, the first five to ten EEG files from each site were manually reviewed for recording quality and isoelectric events, and compared with results from the MATLAB program to reaffirm the program for isoelectric event validity and consistency. Artifacts consisted of at least one channel either disconnected or with an amplitude amplitude greater than 200 μV or less than -200 μV. EEGs with artifact or disconnect greater than 25% of total recordings were excluded from analysis. Artifact-free EEGs were analyzed for isoelectric intervals, defined as amplitude < ±10μV (peak to peak) for 2 s or greater, simultaneously across all four channels, defined *a priori* based on previous pediatric EEG studies.[7,8,14]

Intraoperative Hypotension. Intraoperative systolic arterial pressure and mean arterial pressure (MAP) were recorded every 3 to 5 min per institutional protocols. Recordings outside of systolic arterial pressure 20 to 200 mmHg and MAP 15 to 160 mmHg were discarded as artifact as these values were outside of physiologic norms.[15] If both invasive (arterial line) and noninvasive (cuff) pressures were recorded, arterial line pressures were analyzed. Hypotension criteria was based on population normative values for arterial pressure as defined in patients of similar demographics and geographical locations.[16,17] Hypotension occurred when two or more recordings three or more minutes apart met the following criteria. For patients 6 months or younger, degree of hypotension was graded as mild (systolic arterial pressure 51 to 60 mmHg or MAP 36 to 45 mmHg), moderate (systolic arterial pressure 41 to 50 mmHg or MAP 26 to 35 mmHg), and severe (systolic arterial pressure less than 41 mmHg or MAP less than 26 mmHg).[16,17] For patients older than 6 months, degree of hypotension was graded as mild (systolic arterial pressure 61 to 70 mmHg or MAP 41 to 50 mmHg), moderate (systolic arterial pressure 51 to 60 mmHg or MAP 31 to 40 mmHg), and severe (systolic arterial pressure less than 51 mmHg or MAP less than 31 mmHg).[17] Occurrence and degree of hypotension were only analyzed during preincision and surgical maintenance phases due to artifacts present during induction and emergence.

Emergence Behavior. After airway device removal, the patient was assessed continuously for 15 min by the research team with the modified Watcha score (1, calm or asleep; 2, not calm, but can be consoled; 3, crying, cannot be consoled; and 4, thrashing and inconsolable),[18,19] and the highest score observed during that time was recorded.

Pediatric Quality of Life Questionnaire

The Pediatric Quality of Life questionnaire is a validated and widely used instrument in pediatric research (translated into more than 50 languages) that assesses physical, emotional, and social functioning in children and infants.[20,21] The instrument consists of questions in the following age groups: 1 to 12 months, 36 questions divided into Physical Functioning (6), Physical Symptoms (10), Emotional Functioning (12), Social Functioning (4), and Cognitive Functioning (4); 13 to 24 months, 45 questions divided into Physical Functioning (9), Physical Symptoms (10), Emotional Functioning (12), Social Functioning (5), and Cognitive Functioning (9); and 25 to 36 months, 24 questions divided into Physical Functioning (8), Emotional Functioning (5), Social Functioning (5), and Cognitive Functioning (6). Each question is scored on a 5-point Likert scale. An age-appropriate Pediatric Quality of Life questionnaire was given to the parent or caregiver in their language before surgery on the day of surgery (baseline), 5 days (follow-up No. 1), and 30 days (follow-up No. 2) after surgery.

Statistical Analysis

The estimated sample size was based on two studies observing a 50 to 60% prevalence of isoelectric events in infants and toddlers receiving sevoflurane or propofol for anesthetic maintenance.[7,8] Assuming similar prevalence of isoelectric events internationally, 97 patients were required to reach a margin of error of 0.1 for 95% CI. To target similar prevalence precision across the five age groups, the sample size was multiplied by 5 ($97 \times 5 = 485$). The final target of evaluable patients was 647 ($485 / 0.75 = 647$), to account for a 25% attrition rate related to protocol violations or EEG recording problems.

Demographics were summarized with descriptive statistics. Prevalence of isoelectric EEG events was summarized for the entire recording and the four anesthetic phases, induction, preincision, surgery maintenance, and emergence, as (1) occurrence of isoelectric event(s) (yes or no); (2) number of events; (3) total duration of events (seconds); (4) average duration of each event (seconds); and (5) percentage of total isoelectric duration over recording duration. In patients with isoelectric events, median and interquartile ranges were reported for No. 2 to No. 5.

To account for clustering of isoelectric events within sites, an unconditional generalized linear mixed-effect model, with binomial distribution, logit link function, and site-specific random intercept, was fitted to calculate marginal estimate of isoelectric event prevalence during the entire recording. To determine the anesthetic phase with the highest prevalence of isoelectric events, a generalized linear mixed-effect model growth model with binomial distribution, logit link function, and patient-specific random intercept was fitted. Anesthetic phases and sites were added as fixed effects in this model. *Post hoc* pairwise comparisons between anesthetic phases were conducted ($4 \times 3 / 2 = 6$ tests). To explore whether the prevalence of isoelectric events during anesthetic phases differed by age groups, an interaction term between age group and anesthetic phase was added to the generalized linear mixed-effect model growth model. *Post hoc* contrasts were conducted for the pairwise comparison of anesthetic phases for each age group (5 age groups × 6 pairs = 30 comparisons). The Bonferroni method was used to adjust for multiple comparisons, and simultaneous 95% CIs were calculated.

To identify perioperative variables associated with occurrence of isoelectric events, demographic and anesthetic variables were summarized for patients with and without isoelectric events. Generalized linear mixed-effect models with binomial distribution, logit link function, and site-specific random intercept were used to assess the association between categorical variables and occurrence of isoelectric event, specifying isoelectric event as the dependent variable and categorical variables as the fixed-effect variable. Linear mixed-effect models with site-specific intercept were used to assess the association between continuous variables and occurrence of isoelectric events, specifying continuous variables as dependent variables and isoelectric event (yes or no) as the fixed-effect variable. Continuous variables with right-skewed distribution (*i.e.*, anesthetic duration) were log-transformed and presented with relative mean difference as the effect estimate. Based on editor and reviewer feedback, a *post hoc* subgroup analysis was conducted in patients 0 to 3 months, the age group with the highest prevalence of isoelectric events. Anesthetic variables were compared between 0 to 3 months and older than 3 months patients using similar mixed-effect models, specifying age group as the fixed-effect variable and anesthetic variables as dependent variables.

To explore differences in isoelectric prevalence between sites, the chi-square test was conducted as a global test, and standardized residual was calculated for each site, where absolute values 2 or greater were considered significantly deviated from the expected average isoelectric event prevalence across all sites.[22] We also explored differences in anesthetic variables associated with isoelectric events between sites using the chi-square test for categorical variables and one-way ANOVA for continuous variables. If the global test was significant, *post hoc* analysis was conducted to identify sites with significant deviation from other sites using standardized residual for categorical and pairwise *t* test with Bonferroni correction for continuous variables.

The raw Pediatric Quality of Life score was converted into a 0 to 100 scale (higher score indicated "better" quality of life) if 50% or more items were completed.[23] Pediatric Quality of Life baseline score was subtracted from follow-up No. 1 and No. 2 to calculate changes from baseline. Across three age groups (0 to 12, 13 to 24, and 25 to 36 months), the Wilcoxon rank sum test was used to determine the association between patients with isoelectric events and Pediatric Quality of Life scores at baseline, follow-up No. 1, and No. 2, and changes of follow-up No. 1 and No. 2 from baseline, summarized as median (interquartile range). The difference in Pediatric Quality of Life score between patients with *versus* without isoelectric events was summarized using the Hodges-Lehmann estimator (median of differences and 95% CI). No adjustment for multiple comparisons was conducted for this exploratory analysis. All available Pediatric Quality of Life data were analyzed. A *post hoc* analysis was performed to compare the characteristics between patients with *versus* without complete Pediatric Quality of Life assessments to assess the assumption of missingness at random. Additionally, in patients with complete Pediatric Quality of Life assessments (complete case analysis), a *post hoc* sensitivity analysis of Pediatric Quality of Life scores between patients with *versus* without isoelectric events was conducted.

All analyses conducted were primary analyses of data. The results from subgroup and *post hoc* analyses were not defined *a priori* and should be interpreted as only exploratory. Statistical analyses were performed with R software version 3.5.1. (https://www.r-project.org/, accessed May 23, 2022). Two-tailed testing was conducted for all hypothesis testing, and a *P* value $<$ 0.05 was considered statistically significant.

Results

A total of 708 patients was enrolled to produce 648 evaluable patients from June 2018 to November 2019 (fig. 1). Most patients were ASA Physical Status I or II (94%), born full-term (86%), and underwent general or urological surgery (85%).

Prevalence of Isoelectric EEG

Isoelectric events occurred in 32% (206 of 648) of patients (table 1). In patients who had isoelectric events, the median (interquartile range) number of isoelectric events per patient and duration per event was modest: 13 (4 to 56) events per patient and 4 (3 to 6) seconds per event, although the range was wide (1 to 1,157 events and 2 to 3,277 s per event). The median (interquartile range) percent of total isoelectric time over recording time was 1.1% (0.3 to 4.4). The marginal estimate of isoelectric event prevalence to account for within-site clustering was 31.5% (95% CI, 25.2 to 38.5%), similar to the overall observed prevalence: 31.8%. Therefore, observed prevalence was used for subsequent analyses (fig. 2). The prevalence of isoelectric events was greater during preincision (19%) and surgical maintenance (18%) than induction (9%) and emergence (8%) (table 1). *Post hoc* pairwise comparisons between phases showed that isoelectric events were more likely (odds ratio; 95% CI) during preincision *versus* induction (3.01; 1.72 to 5.3; $P <$ 0.001), surgical maintenance *versus* induction (2.89; 1.65 to 5.0; $P <$ 0.001), preincision *versus* emergence (4.6; 2.49 to 8.5; $P <$ 0.001), and surgical maintenance *versus* emergence (4.4; 2.40 to 8.1; $P <$ 0.001).

There were significant differences in prevalence of isoelectric events among sites (table 2). The prevalence and

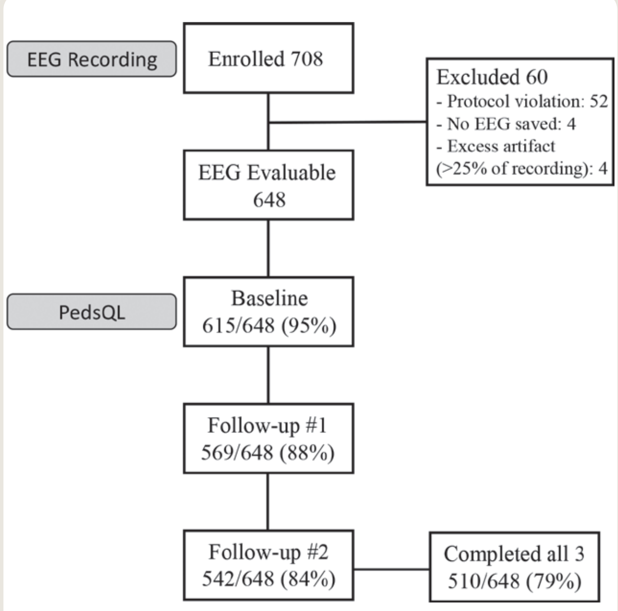

Fig. 1. Strengthening the Reporting of Observational Studies in Epidemiology enrollment diagram for electroencephalography (EEG) recording and completion of Pediatric Quality of Life (PedsQL) questionnaires.

Table 1. Characteristics of Isoelectric Events Overall and across Anesthetic Phases

		Overall	Induction	Preincision	Surgical Maintenance	Emergence
Occurrence of isoelectric events		206 of 648 (31.8%)	54 of 581 (9.3%)	117 of 628 (18.6%)	117 of 643 (18.2%)	42 of 544 (7.7%)
Isoelectric events per patient	Median [interquartile range]	13 [4 to 56]	0 [0 to 1]	1 [0 to 14]	1 [0 to 35.8]	0 [0 to 0]
Total isoelectric time (s)		68.9 [13.7 to 276.7]	0 [0 to 4.2]	3.9 [0 to 58.1]	4.3 [0 to 146.4]	0 [0 to 0]
Isoelectric time per event (s)		3.6 [2.8 to 5.6]	0 [0 to 2.6]	2.6 [0 to 4.2]	2.3 [0 to 4]	0 [0 to 0]
Isoelectric time recording time (%)		1.1 [0.3 to 4.4]	0 [0 to 0.9]	0.4 [0 to 5.5]	0.1 [0 to 2.8]	0 [0 to 0]

Occurrence is number of patients or percent of patients with isoelectric events (%). Isoelectric events per patient is the number of events per patient who had isoelectric electroencephalography.

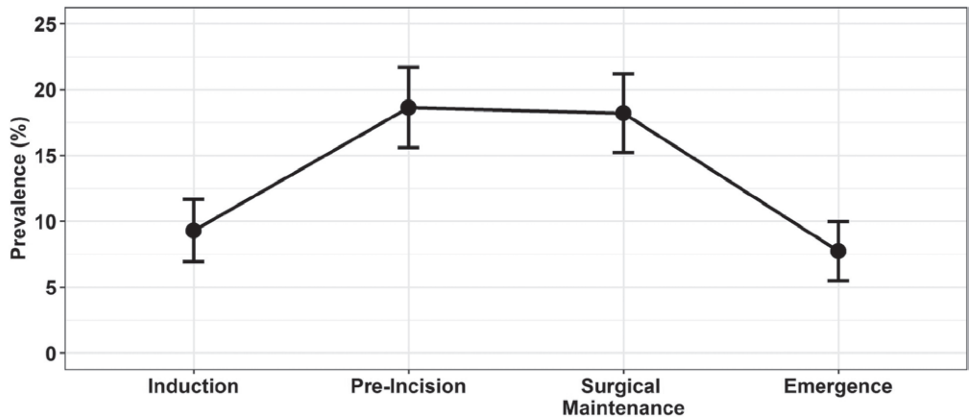

Fig. 2. Prevalence of isoelectric electroencephalography stratified by anesthetic phase. Median (*dot*) and 95% CI (*vertical lines*) displayed.

standardized residual in sites 1 (88%; standardized residual, 3.4) and 5 (44%; standardized residual, 2.0) were significantly higher than the group prevalence, whereas sites 7 (11%; standardized residual, –3.3) and 11 (9%; standardized residual, –2.4) were significantly lower than the group prevalence.

Table 2. Isoelectric Event Occurrence Overall and by Site

Sites	Overall	Isoelectric EEG	Isoelectric %	Standardized Residual
	n = 648	n = 206	31.8	
1	8	7	87.5	3.4*
2	37	9	24.3	–1.0
3	57	22	38.6	1.2
4	55	13	23.6	–1.4
5	52	23	44.0	2.0*
6	46	11	23.9	–1.2
7	53	6	11.3	–3.3*
8	54	17	31.5	–0.1
9	51	22	43.1	1.8
10	52	13	25.0	–1.1
11	23	2	8.7	–2.4*
12	38	14	36.8	0.7
13	22	8	36.4	0.5
14	51	22	43.1	1.8
15	49	17	34.7	0.5

*Indicates standardized residual greater than 2 or less than -2 (significant deviation from group mean).

Demographic and Anesthetic Explanatory Variables

Isoelectric events were most prevalent in the 0 to 3 month group, with odds ratio 4.4 compared to the oldest age group (table 3 and fig. 3). In the 0 to 3 month group, isoelectric events were more likely (odds ratio; 95% CI) to occur during surgical maintenance (18.4; 4.6 to 73.4; $P < 0.001$) and preincision (6.6; 1.73 to 25.5; $P < 0.001$), compared to induction (fig. 3), whereas in the older age groups, occurrence of isoelectric events was similar between the anesthetic phases. The prevalence of isoelectric events was not significantly different between surgery types (table 3).

Occurrence of isoelectric events was associated with certain anesthetic practices (table 4). Isoelectric events were more likely (odds ratio; 95% CI) in patients who received propofol bolus for ETT or laryngeal mask airway placement after sevoflurane induction (2.92; 1.78 to 4.8; $P < 0.001$), and use of ETT *versus* laryngeal mask airway for airway management (1.78; 1.16 to 2.73; $P = 0.008$),

Table 3. Demographics, Surgery Type, and Isoelectric Events

	Overall n = 648	Isoelectric EEG n = 206 (%)	Odds Ratio (95% CI)	*P* Value
Age groups				
0–3 mo	121	71 (59%)	4.4 (2.57–7.5)	< 0.001
4–6 mo	119	31 (26%)	1.05 (0.6–1.85)	0.857
7–12 mo	131	36 (28%)	1.12 (0.65–1.94)	0.671
13–18 mo	127	30 (24%)	0.91 (0.52–1.59)	0.740
19–36 mo	150	38 (25%)	Reference	
Premature birth [54]				
No	514	166 (32%)	Reference	
Yes	80	27 (34%)	1.07 (0.64–1.78)	0.810
ASA Physical Status [13]				
I	329	95 (29%)	Reference	
II	268	96 (36%)	1.42 (0.95–2.13)	0.085
III	38	12 (32%)	1.03 (0.48–2.2)	0.949
Sex [2]				
Male	498	153 (31%)	Reference	
Female	148	53 (36%)	1.30 (0.87–1.94)	0.203
Race/Ethnicity				
White	166	64 (39%)	Reference	
Asian	384	109 (28%)	0.53 (0.29–0.98)	0.042
Other	98	33 (34%)	0.73 (0.42–1.26)	0.256
Surgery type [1]				
General surgery	235	79 (34%)	Reference	
Urology	313	95 (30%)	0.83 (0.56–1.21)	0.327
Other*	99	32 (32%)	0.90 (0.53–1.53)	0.701

Presented as number (n) and percentage of patients (%). [x] represents number of missing values. Generalized linear mixed-effect model was used to adjust for site clustering.
*Other surgeries include plastics, orthopedics, and neurosurgery.
ASA, American Society of Anesthesiologists; EEG, electroencephalography.

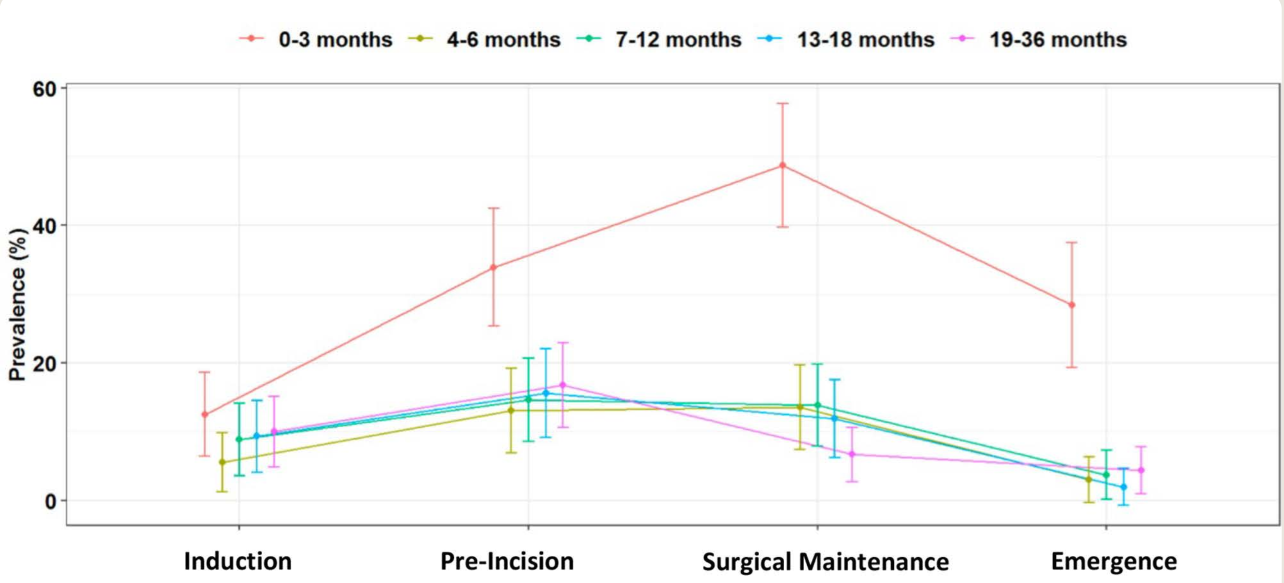

Fig. 3. Prevalence of isoelectric electroencephalography stratified by age groups. Median (*dot*) and 95% CI (*vertical lines*) displayed.

and less likely when a neuromuscular relaxant was administered during induction (0.67; 0.46 to 0.99; $P = 0.046$). In patients who received propofol bolus for IV induction or before airway device placement for sevoflurane induction, the bolus dose (milligram per kilogram) was not related to occurrence of isoelectric events.

Table 4. Anesthetic Variables and Isoelectric Events

		Isoelectric EEG		Generalized Linear Mixed-effect Model/Linear Mixed-effect Model	
	Overall	No	Yes		
	n = 648	n = 442	n = 206	Effect Estimate (95% CI)	*P* Value
Midazolam premedication [6]	119 (19%)	77 (65%)	42 (35%)	1.08 (0.66 to 1.77)	0.754
Sevoflurane induction	387 (60%)	251 (65%)	136 (35%)	1.41 (0.88 to 2.21)	0.151
Propofol IV induction	260 (40%)	190 (73%)	70 (27%)	Reference	
Propofol bolus after sevoflurane induction	160 (41%)	85 (53%)	75 (47%)	2.92 (1.78 to 4.79)	< 0.001
No propofol bolus after sevoflurane induction	226 (59%)	165 (73%)	61 (27%)	Reference	
Propofol bolus dose for IV induction (mg/kg)	3.37 (1.20)	3.31 (1.17)	3.52 (1.27)	0.16 (–0.16 to 0.49)	0.321
ETT airway	452 (70%)	293 (65%)	159 (35%)	1.78 (1.16 to 2.73)	0.008
Laryngeal mask airway	193 (30%)	148 (77%)	45 (23%)	Reference	
Muscular relaxant to intubate [2]	423 (66%)	301 (71%)	122 (29%)	0.67 (0.46 to 0.99)	0.046
Regional anesthesia [3]	259 (40%)	166 (64%)	93 (36%)	1.21 (0.82 to 1.78)	0.331
Opioids [1]	527 (82%)	369 (70%)	158 (30%)	0.72 (0.45 to 1.14)	0.161
Sevoflurane maintenance	359 (55%)	235 (66%)	124 (34%)	1.3 (0.92 to 1.84)	0.137
Propofol maintenance	289 (45%)	207 (72%)	82 (28%)	Reference	
Expired sevoflurane concentration (%) preincision	2.4 (0.8)	2.3 (0.7)	2.6 (0.9)	0.2 (0.1 to 0.4)	0.005
Expired sevoflurane concentration (%) surgical maintenance	2.3 (0.7)	2.3 (0.6)	2.5 (0.7)	0.2 (0.1 to 0.3)	0.002
Systolic arterial pressure mmHg preincision	85 (15)	87 (15)	81 (15)	–5.1 (–7.5 to –2.6)	< 0.001
Systolic arterial pressure surgical maintenance	85 (16)	88 (15)	79 (15)	–7.0 (–9.6 to –4.4)	< 0.001
MAP mmHg preincision	59 (12)	61 (11)	56 (12)	–4.1 (–6.1 to –2.1)	< 0.001
MAP surgical maintenance	59 (12)	61 (12)	54 (11)	–5.3 (–7.3 to –3.3)	< 0.001

Presented as number, percentage of patients (%), or mean (SD). [x] represents number of missing values. Use of midazolam premedication, muscular relaxant to intubate, regional anesthesia, and opioids were compared to without use as reference. The effect estimate is odds ratio for categorical variables, mean difference for normally distributed continuous variables, and relative mean difference for non-normal continuous variables.

EEG, electroencephalography; ETT, endotracheal tube; IV, intravenous; MAP, mean arterial pressure.

Occurrence of isoelectric events was associated with longer anesthetic duration (minutes) (median; interquartile range: 105, 66 to 166 *vs.* 85, 58 to 135; relative mean difference; 95% CI: 1.11; 1.01 to 1.22; $P = 0.024$) and higher expired sevoflurane (%) during preincision and surgical maintenance (table 4). Arterial pressure was also significantly lower in patients with isoelectric events during preincision and surgical maintenance phases, although the absolute differences were small (4 to 7 mmHg). Occurrence of isoelectric events was not associated with induction or maintenance technique (sevoflurane *vs.* propofol; fig. 4).

Given the significantly higher prevalence of isoelectric events in 0 to 3 month *versus* older than 3 months patients, a *post hoc* comparison of anesthetic variables was performed between these two age groups. In the 0 to 3 months group, anesthetic duration was 1.21 times longer than in the older age group (95% CI, 1.09 to 1.36; $P < 0.001$). The 0 to 3 months group were more likely (odds ratio; 95% CI) to have ETT *versus* laryngeal mask airway (7.8; 3.76 to 16.0; $P < 0.001$), or neuromuscular relaxant (2.17; 1.27 to 3.71; $P = 0.004$), and less likely to receive midazolam premedication (0.041; 0.012 to 0.140; $P < 0.001$) and opioid during surgery (0.52; 0.301 to 0.91; $P = 0.021$). Regional anesthesia (odds ratio; 95% CI: 0.84; 0.52 to 1.37; $P = 0.481$), propofol bolus (odds ratio; 95% CI: 1.05; 0.57 to 1.93; $P = 0.878$), or expired sevoflurane (mean difference; 95% CI: during preincision, –0.06; –0.23 to 0.12; $P = 0.513$) or surgical maintenance (–0.09; –0.24 to 0.06; $P = 0.227$) were not significantly different between the two age groups.

Adverse Events and Outcomes Associated with Isoelectric EEG

Mild hypotension was relatively common during preincision (11%) and surgical maintenance (25%), whereas moderate hypotension (2 to 5%) and severe hypotension (2 to 3%) were uncommon (table 5). During preincision, isoelectric events were more common in patients with moderate (odds ratio, 4.6) and severe hypotension (odds ratio, 3.54). During surgical maintenance, isoelectric events were more common in patients with mild (odds ratio, 1.58), moderate (odds ratio, 3.64), and severe hypotension (odds ratio, 7.1). *Post hoc* analysis showed that compared to the older age group (older than 3 months), the 0 to 3 month group was more likely (odds ratio; 95% CI) to have hypotension during preincision (mild: 2.85; 1.57 to 5.2; $P < 0.001$; moderate: 4.6; 1.36 to 15.4; $P = 0.014$; severe: 12.06; 3.95 to 36.81; $P < 0.001$) and surgical maintenance (mild: 1.92; 1.18 to 3.14; $P = 0.009$; moderate: 4.6; 2.10 to 10.2; $P < 0.001$; severe: 3.34; 0.90 to 12.4; $P = 0.071$).

Among 593 patients with available emergence behavior scores, the majority (71%) were calm or asleep during the first 15 minutes of recovery, whereas crying, thrashing,

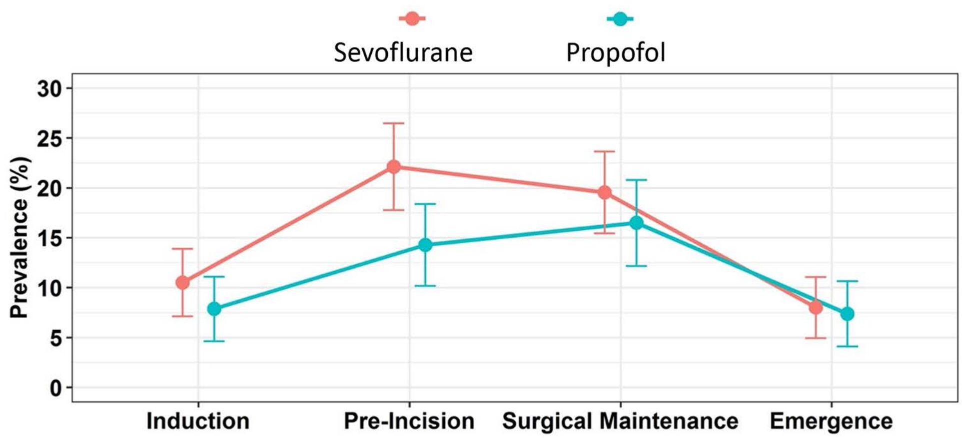

Fig. 4. Prevalence of isoelectric electroencephalography stratified by anesthetic maintenance method and phase. Median (*dot*) and 95% CI (*vertical lines*) displayed.

and inconsolable behaviors were rare (1%). Patients with isoelectric events did not appear to have different emergence behaviors (table 6).

Among 648 evaluable patients, 79% completed all three Pediatric Quality of Life questionnaires with 95, 88, and 84% completing baseline, follow-up No. 1, and follow-up No. 2, respectively (fig. 1). Patients with isoelectric events had lower baseline Pediatric Quality of Life scores in the 0 to 12 month and 25 to 36 month groups and lower follow-up No. 2 scores in the 0 to 12 month group (fig. 5). Baseline Pediatric Quality of Life scores in the 0 to 12 month group were (median; interquartile range) 86.1 (71.1 to 92) *versus* 87.5 (79.2 to 95.3) and (median of differences; 95% CI): –3.5 (–6.2 to –0.7; P = 0.008) and in the 25 to 36 month group were 88.5 (80.4 to 94.3) *vs.* 96.9 (91.7 to 100), –6.3 (–10.4 to –2.1; P = 0.003). Pediatric Quality of Life scores at follow-up No. 2 in the 0 to 12 month group were 86.8 (75 to 93.8) *versus* 89.6 (78.5 to 95.8), –2.8 (–4.9 to 0; P = 0.036). Changes in Pediatric Quality of Life follow-up No. 1 and No. 2 from baseline were similar between patients with *versus* without isoelectric events. *Post hoc* analysis of patients with *versus* without complete Pediatric Quality of Life assessments showed that missingness was associated with site and younger age: 0 to 3 month group were less likely to have complete Pediatric Quality of Life compared to the 19 to 36 month group (odds ratio; 95% CI: 0.43; 0.210 to 0.9; P = 0.024). *Post hoc* sensitivity analysis of Pediatric Quality of Life scores in patients who completed all three Pediatric Quality of Life assessments showed similar results to the main analysis, except in the 0 to 12 month group where occurrence of isoelectric events was also associated with lower Pediatric Quality of

Table 5. Isoelectric Events and Hypotension during Preincision and Surgical Maintenance Phases

		Isoelectric EEG		Generalized Linear Mixed-effect Eodel	
	Overall	No	Yes	Odds Ratio (95% CI)	*P* Value
Preincision	n = 602	n = 408	n = 194		
No hypotension	505 (84%)	355 (70%)	150 (30%)	Reference	
Mild	67 (11%)	42 (63%)	25 (37%)	1.36 (0.79 to 2.37)	0.270
Moderate	12 (2%)	4 (33%)	8 (67%)	4.6 (1.30 to 16.1)	0.018
Severe	18 (3%)	7 (39%)	11 (61%)	3.54 (1.27 to 9.9)	0.015
Surgical maintenance	n = 618	n = 420	n = 198		
No hypotension	419 (68%)	307 (73%)	112 (27%)	Reference	
Mild	156 (25%)	96 (62%)	60 (38%)	1.58 (1.04 to 2.39)	0.031
Moderate	32 (5%)	14 (44%)	18 (56%)	3.64 (1.71 to 7.8)	0.001
Severe	11 (2%)	3 (27%)	8 (73%)	7.1 (1.78 to 28.1)	0.005

Presented as number and percentage of patients (%). Degree of hypotension was coded using the most severe hypotension event for each phase for each patient. Each degree of hypotension was compared to no hypotension to derive odds ratio of isoelectric events. Generalized linear mixed-effect model was used to adjust for site clustering.
EEG, electroencephalography.

Table 6. Emergence Behavior Score and Isoelectricity during Anesthesia

Emergence Score	Overall	Isoelectric EEG		Generalized Linear Mixed-effect Model	
		No (Reference)	Yes		
	n = 593	n = 404	n = 189	Odds Ratio (95% CI)	*P* Value
1 Calm or asleep	418 (71%)	277 (69%)	141 (75%)	Baseline	
2 Not calm, but can be consoled	166 (28%)	118 (29%)	48 (25%)	0.86 (0.54 to 1.38)	0.544
3 Crying, cannot be consoled	8 (1%)	8 (2%)	0 (0%)	Not applicable to statistical testing	Not applicable to statistical testing
4 Thrashing and inconsolable	1 (0%)	1 (0%)	0 (0%)	Not applicable to statistical testing	Not applicable to statistical testing

Presented as number and column percentage of patients (%).
EEG, electroencephalography.

Life in follow-up No. 1 (median; interquartile range: 84.0; 71.9 to 91.7; *versus* 86.8; 76.4 to 95.8; median of differences; 95% CI: –3.5; –6.3 to –0.7; $P = 0.016$), suggesting lower Pediatric Quality of Life scores on all three Pediatric Quality of Life questionaries in the 0 to 12 month group with isoelectric events.

Isoelectric EEG Prevalence among Sites

Given the variables that were significantly associated with isoelectric events and the difference in prevalence of isoelectric events among the sites, a *post hoc* analysis compared the high and low prevalence sites (standardized residual outside of ±2) with the average prevalence sites. Higher than average prevalence sites 1 and 5 during surgical maintenance had higher expired sevoflurane concentration (mean ± SD: 2.7% ± 0.4 *vs.* 2.3% ± 0.7; group average) and a higher proportion of patients with mild hypotension (sites 1 and 5: 63% and 42% *vs.* 25%; group average; $P = 0.015$ and $P = 0.003$, respectively). Conversely, lower than average prevalence sites 7 and 11 during surgical maintenance had a higher proportion of patients who did not experience hypotension (sites 7 and 11: 92% and 91% *vs.* 68%; group average; $P < 0.001$ and $P = 0.018$, respectively). The proportion of 0 to 3 month infants and other demographic, anesthetic, adverse event, and outcome variables were not significantly different among the high, low, and average prevalence sites.

Discussion

In this international study of infants and toddlers undergoing common surgical procedures using sevoflurane or propofol for anesthesia induction and maintenance, we

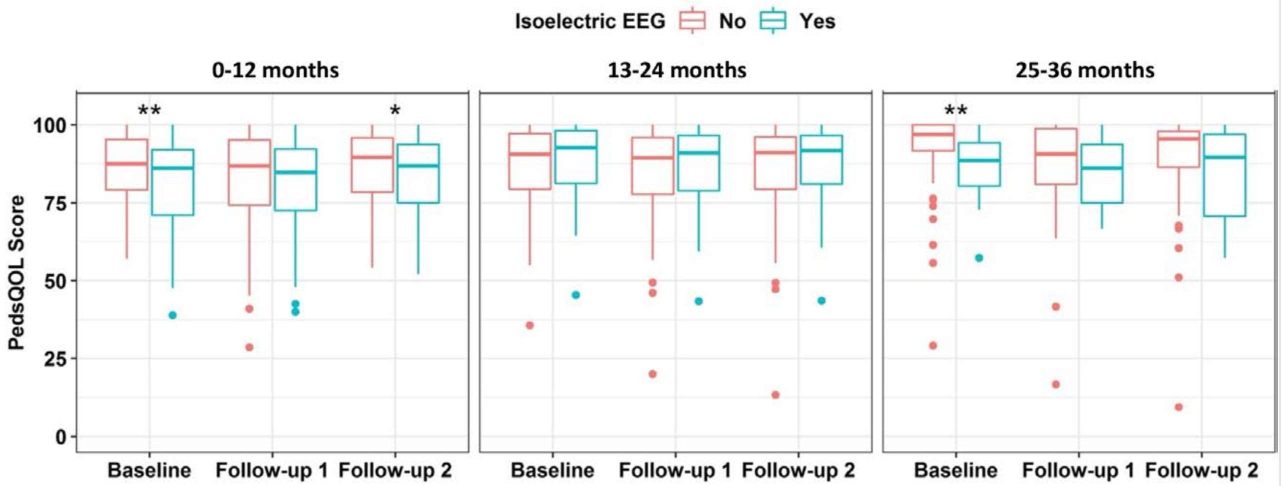

Fig. 5. Association of isoelectric events with Pediatric Quality of Life questionnaire score (0 to 100: the higher the score, the "better" the quality of life). The *solid line* represents the median, *box* the interquartile ranges, *whiskers* 1.5 times length of each quartile, and *dots* the outliers. Comparisons were made using Wilcoxon rank sum between patients with *versus* without isoelectric events. *$P < 0.05$, **$P < 0.01$. EEG, electroencephalography.

found that occurrence of isoelectric events were (1) common worldwide (32%) with large variation across sites (9 to 88%); (2) more common during preincision and surgical maintenance; (3) associated with younger age (0 to 3 months), use of ETT, propofol for intubation instead of a muscle relaxant, and higher expired sevoflurane during preincision and surgical maintenance; and (4) associated with intraoperative hypotension in all ages and lower Pediatric Quality of Life scores in some age groups, but not with emergence behavior. These findings point to certain pediatric anesthetic practices that may predispose infants and toddlers to isoelectric events and hypotension.

Previous single-center studies found the prevalence of isoelectric events ranged from 51 to 63%.[7,8] Although isoelectric events were less common on average in our study, the incidence remained substantial (32%) with some sites higher (88%) and others lower (8%). The prevalence of isoelectric events was associated with differences in certain anesthetic practices (*e.g.,* use of muscle relaxant for intubation). Our study was not designed to determine the reason for the variation among sites, and therefore, the *post hoc* analysis should be considered exploratory due to unknown confounding factors. Nevertheless, sites with a higher than average prevalence of isoelectric events had higher expired sevoflurane and a higher proportion of patients with hypotension during surgical maintenance phase, whereas sites with a lower than average prevalence of isoelectric events had a lower proportion of patients with hypotension.

Isoelectric EEG is indicative of a marked reduction in brain synaptic activity and metabolism,[24] which can be due to encephalopathies, hypoxic ischemic injury, trauma, hypothermia, or certain drugs such as anesthetics.[25,26] Isoelectric EEG can also be seen in preterm infants as part of normal neurodevelopment, but is typically not seen after 38 weeks' gestational age.[25] Therefore, the isoelectric events in our cohort can be mainly attributed to the effects of propofol and sevoflurane, reflecting a deep state of anesthesia and possibly an "over-anesthetized" brain.[27] The pharmacology of sevoflurane and propofol are different, and therefore, their mechanism of producing isoelectricity may differ as the brain matures.[28] Consequently, the effect of isoelectricity on outcomes may very well be different by drug and age.[28–30]

Isoelectric events were 2.92 times more likely when a propofol bolus was administered for intubation or laryngeal mask airway placement after sevoflurane induction, and 0.67 times less likely when muscle relaxant was used for intubation. It is not uncommon to administer a propofol bolus for intubation after sevoflurane induction to prevent laryngospasm, rather than administer a muscle relaxant. Based on our results, it would appear that this practice is associated with an isoelectric neocortex and hypotension.[31,32] Our study did not find a difference in prevalence of isoelectric events between maintenance with sevoflurane or propofol infusion, which is different from a study by Rigouzzo *et al.* that showed more isoelectric events with propofol infusion in children older than 5 yr.[28] Our different results might be explained by our younger study population.

Across all age groups, occurrence of isoelectric events was associated with higher expired sevoflurane during preincision and surgical maintenance, although the difference in expired sevoflurane (0.2%) remains within the range of normal practice and biologic variation of minimum alveolar concentration. Thus, without EEG monitoring, it would be difficult to prescribe a dose of sevoflurane for surgical maintenance that would reliably avoid isoelectricity. If prevention of isoelectricity is an objective of the anesthetic, using a muscle relaxant for intubation and adjusting the sevoflurane or propofol dose based on EEG activity may be associated with less isoelectricity. It is also common to induce anesthesia with high doses of sevoflurane to rapidly achieve "deep" anesthesia to avoid airway complications associated with "light" anesthesia. The continued use of this sevoflurane dose during the surgical maintenance phase should be scrutinized to avoid isoelectric EEG and associated hypotension. These recommendations are consistent with previous studies and provide modifiable factors to prevent isoelectric events.[7,8,14,29,33]

Although propofol and sevoflurane are known to induce isoelectricity, it was surprising that our study did not find an association between the prevalence of isoelectricity and the bolus dose of propofol. Biologic variability in the dose response to induce isoelectricity and the narrow propofol dose range administered (patients with versus without isoelectric events: mean ± SD: 2.5 ± 1.1 mg/kg *vs.* 2.5 ± 1.2; mean difference, 0.2; $P = 0.263$) likely explain this observation. In addition, the propofol dose to induce isoelectricity in children appears to be much higher than the dose reported in this study.[28]

The youngest group (0 to 3 months) was 4.4 times more likely to experience isoelectric events compared to the oldest group (19 to 36 months). This is consistent with previous studies and may reflect the sensitivity of the young brain to anesthetics or to age related pharmacokinetic differences.[6–8,29,34] In the *post hoc* analysis, the expired sevoflurane concentration was not statistically different between the 0 to 3 month *vs.* older than 3 months groups, suggesting that differences in expired sevoflurane concentration was not the etiology; perhaps the younger brain (0 to 3 months) does not require the same amount of anesthetic as the older brain (older than 3 months) to experience isoelectricity. This conclusion should be tempered against the possibility that sevoflurane expired concentration may not reflect alveolar or brain concentration in the youngest age group due to sampling difficulties at low tidal volumes and high ventilatory rates.

Isoelectric EEG during anesthesia has been associated with intraoperative hypotension, postoperative delirium, and postoperative cognitive dysfunction in adults.[3–5] In neonates undergoing cardiac surgery, longer duration of isoelectric events was associated with worse long-term neurologic outcomes.[30] No association between isoelectric events and emergence delirium behavior was found in this study or previous pediatric studies,[6,8] although the patients in our study (36 months or younger) may be too young to truly display emergence delirium as described in older children.

In pediatric anesthesia, intraoperative hypotension is a critical event[35] and can lead to cerebral desaturation,[16] postoperative seizures, and watershed cerebral ischemia if hypotension is sufficiently long and severe.[36] Our study showed that patients with isoelectric events had statistically lower arterial pressures compared to patients without isoelectric events, although the absolute difference in arterial pressure was small (MAP differences of 4 to 5 mmHg) with unclear clinical significance. Of concern, during surgical maintenance, isoelectric events were associated with moderate (odds ratio, 3.64) and severe hypotension (odds ratio, 7.1). However, we were not able to discern the causal or temporal relationship between occurrence of isoelectric events and hypotension, since arterial pressures were measured much less frequently than isoelectric EEG events (minutes *vs.* seconds).

The Pediatric Quality of Life questionnaire is a validated and extensively used instrument in evaluating pediatric patient outcomes after a wide range of pediatric surgeries.[20,21,37,38] We used this instrument to explore the short-term outcome of isoelectric EEG events during anesthesia. We found that patients with isoelectric events had worse Pediatric Quality of Life scores at baseline in the 0 to 12 month and 24 to 36 month groups and at 30 days after surgery in the 0 to 12 month group. However, changes in Pediatric Quality of Life from baseline to follow-up No. 1 and No. 2 were similar between patients with *versus* without isoelectric event, suggesting that after accounting for baseline Pediatric Quality of Life differences, the association between intraoperative isoelectric events and Pediatric Quality of Life at 30 days after surgery may not be significant. The difference in baseline Pediatric Quality of Life scores between patients with and without intraoperative isoelectric events may be due to the underlying patient disease or condition for the surgery that created a predisposition to isoelectric EEG during anesthesia.

Study Limitations

This was an observational study, and thus, associations do not imply causation. It is possible that unknown confounding factors could explain some of the associations. Accordingly, our study does not offer real evidence to recommend changes in clinical practice, but rather raises questions about some of our current anesthetic practices in infants and toddlers for further study.

This was a pragmatic study to determine the prevalence of isoelectric events in a real-world situation, and therefore, the anesthetic technique was not standardized; some patients induced with sevoflurane in the propofol infusion maintenance group may still have residual sevoflurane after intubation. Despite filtering for EEG artifact during isoelectric EEG analysis, motion artifact, particularly during induction and emergence, could still be present and result in undercounting of isoelectric events. Unlike sevoflurane dosing (*e.g.*, expired sevoflurane percentage), propofol infusion dosing could not be recorded and compared because of practice differences in the use of manual infusion and target-controlled infusion among the sites. Gestation-adjusted age was not used for assigning patients into age groups, although the percentage of premature children was small (13.5%) and unlikely to affect our results. There was a high proportion of Asian children (59.3%) in the study; this was to be expected since 7 out of 15 sites were in China. We could not determine whether race or ethnicity or practice pattern contributed to the prevalence of isoelectric EEG since there was a disproportional distribution of race or ethnicity between sites.

The Pediatric Quality of Life outcome was exploratory with limitations in interpretating the data. There was a mismatch between the five age groups for EEG recording and three age groups for the Pediatric Quality of Life due to the design of the Pediatric Quality of Life instrument. In addition, Pediatric Quality of Life scores were not normally distributed, which impacted the ability to fully account for baseline Pediatric Quality of Life differences on the follow-up scores in the isoelectric and non-isoelectric groups. Finally, we could not eliminate two biases from the study: response bias from the parents or caregivers completing the Pediatric Quality of Life survey, although we determined that missingness was systematically related to site and age, and observer bias from the anesthesia provider caring for the patient despite the provider being blinded to the EEG waveforms during the study.

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Competing Interests

Dr. Yuan and Dr. Kurth received speaker honoraria from Masimo Inc. Dr. Kurth served on the advisory board of

Masimo Inc. Dr. von Ungern-Sternberg disclosed a financial relationship with StanPerron Charitable Foundation (Perth, Australia). Dr. Davidson and Dr. Vutskits serve on the editorial board of Anesthesiology. The other authors declare no competing interests.

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Appendix

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